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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,534	06/09/2006	Zheng Xin Dong	140P/PCT2/US	9889

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
06/30/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,534	DONG, ZHENG XIN	
	Examiner	Art Unit	
	DAVID LUKTON	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-12 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Pursuant to the response filed 4/14/10, claims 3-12, 14 are now pending.

✧

Claims 3-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of 7268213. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d).

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have submitted a declaration which supports the proposition that the claimed compounds will displace (^{125}I) GLP-1(7-36) from RIN 5F rat

insulinoma cells expressing the GLP-1 receptor. Claims which are drawn to compounds *per se* are not now being rejected for lack of enablement. But the first question is, are the claimed compounds agonists or antagonists of the GLP-1 receptor? One cannot know the answer to this based only on the binding data. It could very well be the case that the claimed peptides are actually antagonists of the GLP-1 receptor, in which case they will exhibit pharmacological effects which are opposite to that which applicants are hoping for. Consider, for example, the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) **55** (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo*

activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) **2** (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [^{125}I]-Nle^{4}-D-Phe^{7}-*alpha*-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

- Miyagi, M. (*Biol Pharm Bull* 19, 1210-13, 1996) discloses that bromocriptine binds to the D1 and D2 receptor, but is inactive *in vivo*.

So it may well be the case that the claimed peptides are not agonists at all (but are antagonists). And suppose, at some point in the future, applicants are able to show that, e.g., cAMP production *in vitro* is stimulated by the presence of one of the claimed peptides. Would this necessarily mean that the peptides will be effective to treat diabetes?

In response to the foregoing, applicants have made several arguments, beginning with the proposition that an invention may be enabled if other practitioners are able to "duplicate …[the] efforts" of the inventor. However, applicants do not know whether the claimed compounds will ameliorate symptoms of diabetes, or exacerbate them, or have no effect at all.

Applicants have also argued that the examiner has "accused" applicants of failing to provide evidence that cAMP production is increased or decreased as a consequence of binding one of the claimed peptides to cells bearing the GLP-1 receptor. Selection of the term "accused" would seem unnecessary, but it is an uncontested fact that applicants have not provided this information. Nor does the examiner argue that this data is **necessarily** a requirement for a finding that claims 12 and 14 might be enabled. For example, there are animal models of diabetes which applicants could use (not that the examiner is necessarily arguing that such animal models are necessarily required, either).

Next, applicants have begun with the premise that the examiner has imposed a rejection for lack of utility, and have proceeded to argue that a rejection for lack of utility might not be valid. However, the examiner has not imposed a rejection for lack of utility, and so the issue is moot.

Next, applicants have argued that GLP-1 itself is known in the art to exhibit pharmacological activity, and therefore it follows that any peptide which exhibits affinity for the GLP-1 receptor will exhibit the same in vivo activities as GLP-1 itself. Applicants have also argued that a peptide which consists of 30 amino acids, and contains Aib promoted insulin secretion in rats, and that therefore any peptide that contains **more than** 30 amino acids, and exhibits affinity for the GLP-1 receptor, will also promote insulin secretion.

Applicants have, for a second time, set forth the premise that the examiner has imposed a rejection for lack of utility, and have proceeded to argue that a rejection for lack of utility might not be valid. However, the examiner has not imposed a rejection for lack of utility, and so the issue is moot.

Applicants' contention is that the addition of two amino acids to [$Aib^{8,35}$]hGLP-1(7-36) will be benign in effect; the examiner, however, contends that one cannot "predict" the outcome of such.

The rejection is maintained.

✧

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

/David Lukton/

Primary Examiner, Art Unit 1654